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Asymmetric Conjugate Addition of Acetylacetone to Nitroolefins with Chiral Organocatalysts Derived from Both α-Amino Acids and Carbohydrates

Xuewei Pu,[a] Penghui Li,[a] Fangzhi Peng,[a] Xiaojiao Li,[a] Hongbin Zhang,[a] and Zhihui Shao*[a,b]

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Bifunctional chiral tertiary amine thioureas derived from both α-amino acids and carbohydrates were developed. These organocatalysts promoted the enantioselective conjugate addition of acetylacetone to various aromatic and aliphatic nitroolefins at room temperature in good yields (up to 93%) and with good enantioselectivity (up to 90% *ee*). Furthermore, an interesting matched–mismatched effect of two different chiral units in a chiral organocatalyst was disclosed. Both enantiomers of a product can be achieved in almost the same enantiomeric excess with the "matched" and "mismatched" chiral organocatalysts simply by changing the solvent from THF to toluene.

Introduction

Design of chiral organocatalysts for efficient asymmetric transformations has become a focal point of attention in current asymmetric organocatalysis.[1] Impressive progress has been made in the development of new, readily available, and finetunable chiral organocatalysts. In this regard, we recently developed two new classes of bifunctional chiral organocatalysts bearing two different types of stereogenic structures in a single molecule for promoting asymmetric conjugate addition reactions[2a] and aldol reactions.[2b] Our continuous interest[3,4] in developing easy-to-prepare, cheap, and finetunable chiral organocatalysts prompted us to explore new catalyst design strategies.

Acyclic α-amino acids have been proven to be useful chiral scaffolds and have been extensively applied in the preparation of chiral organocatalysts as a result of the availability of both enantiomers.[5] In contrast, carbohydrates have received less attention[6] in the design of chiral organocatalysts, although they are potential chiral scaffolds for the synthesis of chiral organocatalysts. Carbohydrates (i.e., monosaccharides) are conformationally stable, cheap, and readily available. In addition, they possess multiple chiral centers and functional groups for catalyst performance optimization. Given these facts, the rational combination of stereocontrolling elements of both α-amino acids and carbohydrates in a single molecule would lead to a new series of cost-effective, finetunable, chiral organocatalysts. Quite surprisingly, chiral organocatalysts with this combined strategy are few. Recently, Kunz and co-workers pioneered the use of carbohydrates in the development of chiral organocatalyst by designing a novel and elegant class of bifunctional Schiff base organocatalysts that catalyzed enantioselective Strecker and Mannich reactions.[6a] Inspired by this pioneering work, we designed and synthesized a new class of chiral bifunctional tertiary amine–thiourea organocatalysts[7] (Figure 1). To the best of our knowledge, no chiral amine–thiourea organocatalyst designed by combining both α-amino acids and carbohydrates has been reported so far. The catalytic activities of these catalysts were evaluated in the asymmetric conjugate addition of acetylacetone to nitroolefins.[8,9] Newly designed organocatalyst **1a** derived from L-valine and D-glucopyranose was shown to be quite effective in the enantioselective conjugate addition of acetylacetone to various aromatic and aliphatic nitroolefins in THF at room temperature in good yields (80–88%) and with good enantioselectivity (80–89% *ee*). Furthermore, we have described an interesting matched–mismatched effect of two different chiral units in a chiral organocatalyst. Both enantiomers of each product can be achieved in almost the same enantiomeric excess with the "matched" and "mismatched" chiral organocatalysts simply by changing the solvent from THF to toluene. In this paper, we wish to report these research results.

[a] Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, P. R. China
[b] School of Chemistry and Biotechnology, Yunnan Nationalities University, Kunming 650031, P. R. China
Fax: +86-871-5035538
E-mail: zhihui_shao@hotmail.com
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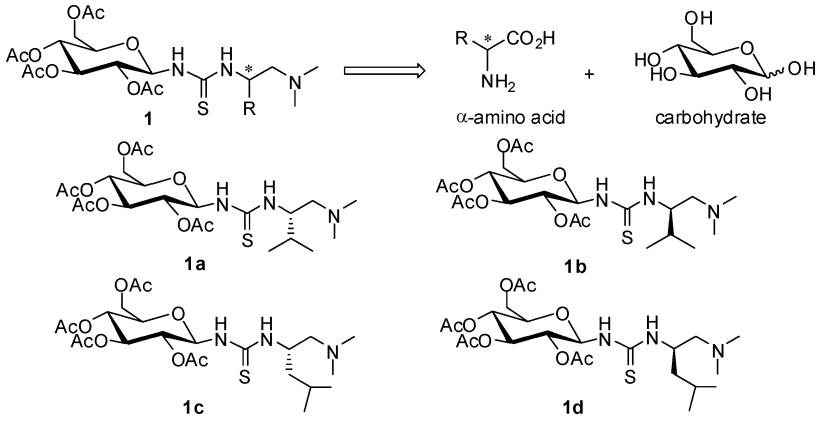
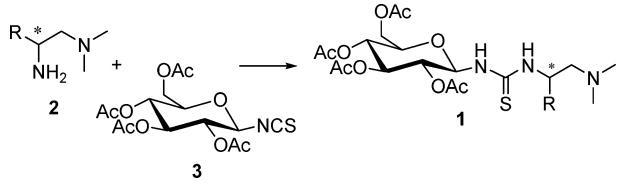


Figure 1. Key design elements of a new class of chiral tertiary amine–thiourea organocatalysts.

Results and Discussion

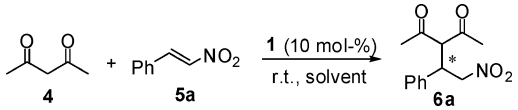
Organocatalysts **1** were easily synthesized by coupling primary–tertiary diamine **2**[10] derived from α-amino acids and isothiocyanate **3**[11] derived from D-glucopyranose (Scheme 1).



Scheme 1. Synthesis of chiral amine–thiourea organocatalysts **1a**–**d**.

The catalytic activity of these chiral amine–thioureas was initially evaluated in the conjugate addition reaction of acetylacetone (**4**) to *trans*-β-nitrostyrene **5a** in the presence of 10 mol-% of catalyst at room temperature, and the results are summarized in Table 1. Five different solvents with organocatalyst **1a** derived from L-valine and D-glucopyranose were examined to find optimum reaction media, and the conjugate addition reaction with organocatalyst **1a** in THF afforded the best enantioselectivity (85%*ee*; Table 1, Entry 5). Next, the conjugate reaction with organocatalyst **1b** derived from D-valine and D-glucopyranose in THF was carried out to investigate the "matched–mismatched" effect of two different chiral units in catalyst **1b**. The use of organocatalyst **1b** in THF provided product **6a** with lower enantioselectivity (76%*ee*; Table 1, Entry 6), as well as a reversal of the absolute configuration of product **6a**. These results indicate that the chiral unit derived from α-amino acids predominates over the absolute configuration of product **6a**. In addition, it seems to indicate that the L configuration of valine matched the D-glucopyranose, enhancing the stereochemical control, whereas the D configuration of valine mismatched the D-glucopyranose. However, such a conclusion is not always right. We were pleased to find that the conjugate reaction with so-called "mismatched" organocatalyst **1b** in *toluene* gave desired product **6a** in almost the same enantiomeric excess with opposite absolute configuration (86% *ee*; Table 1, Entry 7). From a synthetic perspective, both enantiomers of a chiral compound may often be required in organic synthesis and in the pharmaceutical industry. Therefore, discovery of a novel approach for the catalytic asymmetric synthesis of both enantiomers would be highly desirable. This interesting finding might provide a novel approach to obtain both enantiomers of a chiral compound. At the same time, it might have useful implications, especially in screening organocatalysts for asymmetric reactions. Then, the effect of the variation of α-amino acids was briefly studied by using **1c** and **1d** as the catalysts in THF and toluene as solvents, respectively. The reactions were investigated with organocatalyst **1c** derived from L-leucine and D-glucopyranose as well as organocatalyst **1d** derived from D-leucine and D-glucopyranose in THF and toluene, respectively; product **6a** was afforded in lower enantiomeric excess (Table 1, Entries 8–11).

Table 1. Enantioselective addition of acetylacetone (**4**) to *trans*-β-nitrostyrene (**5a**) catalyzed by **1a**–**d**.[a]



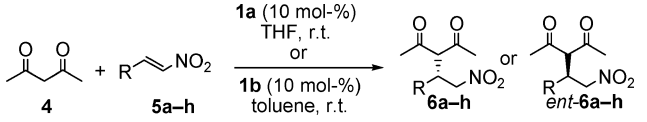
Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	DMF		75	27 (*S*)
2	**1a**	Et_2O		72	73 (*S*)
3	**1a**	DCM		84	82 (*S*)
4	**1a**	toluene		90	82 (*S*)
5	**1a**	*THF*		88	*85 (S)*
6	**1b**	THF		87	76 (*R*)
7	**1b**	*toluene*		90	*86 (R)*
8	**1c**	THF		89	80 (*S*)
9	**1c**	toluene		90	78 (*S*)
10	**1d**	THF		86	74 (*R*)
11	**1d**	toluene		89	79 (*R*)

[a] The reaction was performed with **4** (2 equiv.) and **5a** (1 equiv.) in the presence of catalyst (10 mol-%) at room temperature. [b] Yields of isolated products. [c] Enantiomeric excess values were determined by chiral HPLC analysis (Chiralpak AS-H).

With the optimal reaction conditions in hand, we further studied the generality of the asymmetric conjugate addition reactions of **4** to nitroolefins **5a**–**h** in the presence of cata-

lysts **1a** and **1b**, and the results are shown in Table 2. Both catalysts exhibited good enantioselectivity in the asymmetric conjugate addition reactions. Generally, both enantiomers of a product could be achieved in almost the same enantiomeric excess with catalyst **1a** in THF and with catalyst **1b** in toluene, respectively (Table 2, Entries 1–8). The use of organocatalyst **1a** always gave conjugate adducts **6a**–**h** with (*S*) configuration,[12] whereas the use of organocatalyst **1b** afforded *ent*-**6a**–**h** with the (*R*) configuration.[12] It appears that the position and the electronic property of the substituents for aromatic rings of nitroolefins **5a**–**g** are well tolerated by the conjugate addition reactions. Whether electron-withdrawing (Table 2, Entries 2–4), -donating (Table 2, Entries 5–7), or -neutral (Table 2, Entry 1) groups on the aromatic rings were used, the reactions proceeded smoothly to give the desired adducts in good yields (80–93%) and with good enantioselectivity (83–89%*ee*). Notably, the conjugate reactions of aliphatic nitroolefin **5h** with **4** not only worked well in the presence of organocatalysts **1a** and **1b** but also afforded desired product **6h** and *ent*-**6h** with almost the same enantiomeric excess (80%*ee* in THF, 81%*ee* in toluene; Table 2, Entry 8). Few examples of the asymmetric addition of acetylacetone to aliphatic nitroolefins have been described so far as a result of the lower reactivity of aliphatic nitroolefins than aromatic nitroolefins.[2a,9i] The highest enantioselectivity in the asymmetric addition of acetylacetone to aliphatic nitroolefins so far was reported to be 85%*ee*.[9i] During the course of our study, the group of Zhou reported the application of similar chiral tertiary amine–thiourea organocatalysts derived from *trans* cyclohexane-1,2-diamine and D-glucopyranose in the asymmetric conjugate addition of acetylacetone to aromatic nitroolefins.[9k] However, these organocatalysts could *not* catalyze the asymmetric addition of acetylacetone to aliphatic nitroolefins. These results might indicate the advantage of incorporating α-amino acids into chiral tertiary amine–thiourea organocatalysts.

Table 2. Organocatalytic enantioselective conjugate addition of acetylacetone (**4**) to various nitroolefins **5a**–**h** promoted by amine–thioureas **1a** and **1b**.[a]



4 **5a–h** **6a–h** *ent*-**6a–h**

Entry	Catalyst	R	*t* [h]	Yield [%][b]	Product (*ee* [%])[c]
1	**1a**	Ph (**5a**)	17	88	**6a** (85)
	1b		14	90	*ent*-**6a** (86)
2	**1a**	4-ClC_6H_4 (**5b**)	18	80	**6b** (88)
	1b		15	92	*ent*-**6b** (86)
3	**1a**	4-BrC_6H_4 (**5c**)	20	84	**6c** (86)
	1b		15	93	*ent*-**6c** (88)
4	**1a**	2-$CF_3C_6H_4$ (**5d**)	18	80	**6d** (83)
	1b		14	87	*ent*-**6d** (88)
5	**1a**	4-MeC_6H_4 (**5e**)	20	86	**6e** (86)
	1b		20	90	*ent*-**6e** (88)
6	**1a**	4-MeOC_6H_4 (**5f**)	18	82	**6f** (90)
	1b		15	89	*ent*-**6f** (87)
7	**1a**	2-BnOC_6H_4 (**5g**)	36	80	**6g** (85)
	1b		32	87	*ent*-**6g** (88)
8	**1a**	*i*Bu (**5h**)	40	81	**6h** (80)[d]
	1b		48	85	*ent*-**6h** (81)[d]

[a] The reaction was performed with **4** (2 equiv.) and **5a**–**h** (1 equiv.) in the presence of catalyst **1a** or **1b** (10 mol-%) at room temperature. [b] Yields of isolated products. [c] Enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AS-H, AD-H and Chiralcel OD-H). [d] Absolute configuration was not determined.

Conclusions

In summary, we have developed a class of novel and fine-tunable chiral tertiary amine–thiourea organocatalysts derived from commercially available, inexpensive α-amino acids and carbohydrates. These organocatalysts promoted the asymmetric conjugate addition of acetylacetone to various nitroolefins at room temperature in good yields (up to 93%) and with good enantioselectivity (up to 90%*ee*). Furthermore, we described an interesting matched–mismatched effect of two different chiral units in a chiral organocatalyst. Both enantiomers of a product can be achieved in almost the same enantiomeric excess with the "matched" and "mismatched" chiral organocatalysts simply by changing the solvent from THF to toluene. This finding provides a novel approach to obtain both enantiomers of a chiral compound. At the same time, it might have useful implications, especially in screening the organocatalysts for asymmetric reactions. Further investigation of the efficacy of these organocatalysts in other catalytic asymmetric reactions and development of the chiral primary amine–thiourea organocatalysts derived from both α-amino acids and carbohydrates are under way in our laboratory.

Experimental Section

General: ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance 300 spectrometer. Chemical shifts (δ) are expressed in ppm, and *J* values are given in Hz. The enantiomeric excess was determined by HPLC (Agilent 1100 series) by using Chiralpak AS-H or AD-H and Chiralcel OD-H column with *n*-hexane and 2-propanol as eluents. High-resolution mass spectra were taken with an AB QSTAR Pulsar mass spectrometer. Optical rotations were obtained with a UV-210A spectrometer. All chemicals and solvents were used as received without further purification unless otherwise stated. Flash column chromatography was performed on silica gel (230–400 mesh).

General Procedure for the Preparation of Catalysts 1a–d: To a solution of primary–tertiary diamine **2** derived from α-amino acids (1 mmol) in dry THF (5 mL) was added dropwise a solution of isothiocyanate **3** derived from D-glucopyranose (1.2 mmol) in dry THF (10 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 35 °C, and the reaction was monitored by TLC. After removal of the solvent, the residue was purified by column chromatography on silica gel to give the amine–thiourea catalysts.

(4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-{3-[(*S*)-1-(dimethylamino)-3-methylbutan-2-yl]thioureido}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (1a): Yield: 431 mg (83%). $[\alpha]_D^{20}$ = –9.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.15 (br. s, 1 H), 5.74 (t, *J* = 8.8 Hz, 1 H),

5.32 (t, J = 9.5 Hz, 1 H), 5.07 (t, J = 9.7 Hz, 1 H), 4.93 (t, J = 9.3 Hz, 1 H), 4.26 (dd, J = 4.1, 3.9 Hz, 1 H), 4.15 (dd, J = 2.0, 2.3 Hz, 1 H), 3.88 (m, 1 H), 3.28 (br. s, 1 H), 2.50–2.46 (m, 2 H), 2.32 (s, 6 H), 2.04 (s, 6 H), 2.02 (s, 6 H), 1.83 (m, 1 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.0, 170.5, 170.1, 169.8, 83.9, 73.3, 71.3, 68.5, 63.5, 61.9, 59.7, 44.9, 31.5, 20.8, 20.6, 18.1, 18.0 ppm. HRMS (FAB+): calcd. for $C_{22}H_{38}N_3O_9S$ [M + 1]$^+$ 520.232877; found 520.232998.

(4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-{3-[(*R*)-1-(dimethylamino)-3-methylbutan-2-yl]thioureido}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (1b): Yield: 420 mg (81%). $[\alpha]_D^{20}$ = +44.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.76 (m, 1 H), 5.23 (t, J = 9.4 Hz, 1 H), 5.01 (t, J = 9.6 Hz, 1 H), 4.87 (t, J = 9.4 Hz, 1 H), 4.18 (d, J = 12.3 Hz, 1 H), 4.06 (d, J = 12.4 Hz, 1 H), 3.76 (m, 1 H), 2.63–2.37 (m, 2 H), 2.24 (s, 6 H), 1.99 (s, 3 H), 1.98 (s, 3 H), 1.96 (s, 3 H), 1.94 (s, 3 H), 1.19 (m, 1 H), 0.88 (d, J = 4.5 Hz, 3 H), 0.81 (d, J = 2.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.1, 170.6, 170.3, 169.9, 169.7, 83.6, 76.6, 73.5, 73.4, 71.3, 68.4, 62.0, 45.1, 31.6, 20.8, 20.7, 20.6, 18.1 ppm. HRMS (FAB+): calcd. for $C_{22}H_{38}N_3O_9S$ [M + 1]$^+$ 520.232877; found 520.232996.

(4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-{3-[(*S*)-1-(dimethylamino)-4-methylpentan-2-yl]thioureido}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (1c): Yield: 426 mg (80%). $[\alpha]_D^{20}$ = –9.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.16 (br. s, 1 H), 5.71 (br. s, 1 H), 5.33 (t, J = 9.5 Hz, 1 H), 5.08 (t, J = 9.7 Hz, 1 H), 4.94 (t, J = 9.5 Hz, 1 H), 4.28 (dd, J = 3.6, 3.4 Hz, 1 H), 4.15 (d, J = 12.3 Hz, 1 H), 3.88 (m, 1 H), 3.53 (br. s, 1 H), 2.57–2.41 (m, 2 H), 2.33 (s, 6 H), 2.08 (s, 3 H), 2.05 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.68 (m, 1 H), 1.36–1.22 (m, 2 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.90 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.0, 170.6, 169.8, 168.7, 168.6, 83.8, 73.3, 73.1, 71.3, 68.5, 66.9, 61.9, 53.4, 45.1, 42.5, 24.7, 22.7, 20.7 ppm. HRMS (FAB+): calcd. for $C_{23}H_{40}N_3O_9S$ [M + 1]$^+$ 534.248527; found 534.245652.

(4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-{3-[(*R*)-1-(dimethylamino)-4-methylpentan-2-yl]thioureido}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (1d): Yield: 426 mg (80%). $[\alpha]_D^{20}$ = +41.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81 (m, 1 H), 5.33 (t, J = 9.4 Hz, 1 H), 5.08 (t, J = 9.7 Hz, 1 H), 4.96 (t, J = 9.1 Hz, 1 H), 4.28 (dd, J = 4.3, 4.3 Hz, 1 H), 4.12 (d, J = 12.3 Hz, 1 H), 3.86 (m, 1 H), 2.70–2.18 (m, 8 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 2.01 (s, 3 H), 1.69 (m, 1 H), 1.26 (m, 2 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.4, 170.6, 169.9, 169.7, 83.2, 73.4, 71.2, 68.5, 66.1, 62.0, 52.8, 45.2, 42.6, 24.9, 22.7, 20.7, 20.6 ppm. HRMS (FAB+): calcd. for $C_{23}H_{40}N_3O_9S$ [M + 1]$^+$ 534.248527; found 534.245654.

General Procedure for the Asymmetric Conjugate Addition Reaction of Acetylacetone (4) to Nitroolefins 5 Catalyzed by Catalyst 1a or 1b: Catalyst **1a** or **1b** (10.4 mg, 0.02 mmol, 10 mol-%) was added to a vial containing **4** (40 mg, 0.4 mmol) and **5** (0.2 mmol) in dry THF or toluene (0.6 mL) at room temperature. The resulting mixture was stirred at room temperature, and the reaction was monitored by TLC. The reaction mixture was quenched with 1 M aqueous HCl solution, extracted with EtOAc, and dried with Na_2SO_4. The crude product was purified by flash silica gel chromatography to give desired adducts **6**. The *ee* values were determined by chiral HPLC analysis.

Supporting Information (see also the footnote on the first page of this article): NMR spectroscopic data and chiral HPLC data of **6a**–**h**.

Acknowledgments

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